REMARKS

The Examiner rejected claims 1, 6-11, 23, and 25. In light of the following remarks, Applicant respectfully requests reconsideration and allowance of claims 1, 6-11, 23, and 25.

Initialed PTO Forms 1449

Applicant notes that Supplemental Information Disclosure Statements and PTO Forms 1449 were submitted to the United States Patent & Trademark Office on March 22, 2002 and November 13, 2003. To date, however, initialed copies of these forms have not been returned to Applicant's agent. Applicant respectfully requests that the Examiner review the cited documents and return copies of the initialed forms to the undersigned representative.

Rejections under 35 U.S.C. § 103

The Examiner rejected claims 1, 6-11, and 23 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 6,197,789 (the Grainger *et al.* patent). The Examiner stated that the Grainger *et al.* patent teaches that tamoxifen is useful to prevent or treat conditions characterized by inappropriate or pathological activity of endothelial cells. The Examiner also stated that the Grainger *et al.* patent teaches that tamoxifen is useful to inhibit the activation of endothelial cells associated with vascular surgery, diabetes, hypertension, and coronary artery blockage. The Examiner further stated that the Grainger *et al.* patent teaches that procedural vascular traumas and pathologies such as atherosclerosis, myocardial infarction, and stroke can be prevented by administration of tamoxifen. Thus, the Examiner concluded that it would have been obvious to one of ordinary skill in the art to modify the teaching of Grainger *et al.* and employ tamoxifen to normalize the contractile response of vasculature, since the teaching of "inhibiting contraction" encompasses "normalization," and since the effect of inhibition of contraction of vascular smooth muscle would "normalize" the contraction in patients as disclosed by Grainger *et al.*

Applicant respectfully disagrees. The Grainger *et al.* patent fails to render the present claims obvious. First, the Grainger *et al.* patent does not teach or suggest all of the elements of the claims. Specifically, the Grainger *et al.* patent does not suggest using tamoxifen to normalize

the contractile response of vasculature having a vascular smooth muscle cell (VSMC) layer and a compromised endothelial cell layer.

The Examiner agrees with this assertion, as the Office Action of November 30, 2004 at page 3 states that "Grainger *et al.* do not expressly teach the normalization of contractile response set forth in claim 1." Rather, the Grainger *et al.* patent discloses a therapeutic method for preventing or treating a cardiovascular or vascular indication characterized by a decreased lumen diameter, wherein a therapeutic agent that elevates the level of TGF-β is employed (column 2, line 37 to column 3, line 2 and column 10, lines 44-46). The Grainger *et al.* patent also discloses that such an agent can inhibit the activity of a VSMC, such as proliferation, contraction, and migration (column 17, lines 41-48), as well as inhibit the "pathological" or "abnormal" activity of VSMC (column 3, lines 17-22 and column 6, lines 15-16), defined by Grainger *et al.* as "division, growth or migration of cells occurring more rapidly or to a significantly greater extent than typically occurs in a normally functioning cell of the same type, or in lesions not found in healthy tissues" (column 7, lines 61-65). However, there is nothing the Grainger *et al.* patent that teaches or suggests normalizing the contractile response of endothelially-compromised vascular smooth muscle.

Contrary to the Examiner's assertion, the effect of inhibition of contraction of vascular smooth muscle would not necessarily "normalize" the contraction. The Examiner is urged to consider that "inhibition" of VSMC activity is not the equivalent of smooth muscle cell "normalization." Merriam-Webster's online dictionary defines the term "inhibit" as "prohibit from doing something." *See*, Attachment A. In contrast, the term "normalize" is defined by Merriam-Webster's as "reduce to a norm or standard." *See*, Attachment B. The concept of normalization is depicted in Figures 2 and 3 of Applicant's specification, which clearly show that the contractile response of compromised VSM treated with tamoxifen was essentially the same as the contractile response of intact VSM, whether or not the intact VSM was treated with tamoxifen. The compromised VSM treated with tamoxifen was not prohibited from having a contractile response; it was reduced to a normal level. Thus, even if tamoxifen has been suggested to "inhibit" vascular smooth muscle cell contraction, there is nothing in the cited art to suggest that it can correct or normalize the effect contraction endothelially-comprised VSMC. Therefore, the Grainger *et al.* patent does not obviate the pending claims.

Second, the teachings of the Grainger *et al.* patent would not have provided a person of ordinary skill in the art with a reasonable expectation of success for using a compound such as tamoxifen to normalize vasocontraction of compromised vasculature. This is particularly true given that the Grainger *et al.* patent fails to provide any evidence that tamoxifen can affect vasoconstriction. The Grainger *et al.* patent discloses experimental data showing that tamoxifen treatment of VSMC in culture can decrease cell proliferation and increase levels of TGF-beta, while tamoxifen treatment of mice on a high fat diet can reduce the formation of aortic lipid lesions. In fact, the Grainger *et al.* patent is focused on using compounds such as tamoxifen to inhibit proliferation of smooth muscle cells. At column 17, lines 41-47, however, the Grainger *et al.* patent discloses the following:

> Consequently, the methods and dosage forms of this aspect of the present invention are useful for inhibiting vascular smooth muscle cells in a mammalian host, employing a therapeutic agent that inhibits the activity of the cell (*e.g.*, proliferation, formation of lipid proliferative lesions, contraction, migration or the like) . . . (emphasis added)

Even if this statement provides some suggestion to use tamoxifen to inhibit contraction of VSM, it provides no reasonable expectation of success for normalizing contraction of VSM. This is especially true given that inhibition of contraction is not equivalent to normalizing contraction, as discussed above. Thus, the teachings of the Grainger *et al.* patent do not provide motivation for a person having ordinary skill in the art to use tamoxifen to normalize contraction of compromised vasculature as recited in the present claims. As such, the Grainger *et al.* patent fails to render the presently claimed methods obvious.

Moreover, at no point does the Grainger *et al.* patent provide any evidence to indicate that tamoxifen has an effect on contractile VSMC (i.e., mature, non-proliferative VSMC). A person of ordinary skill in the art would appreciate that contractile and proliferative VSMC serve different purposes, and thus have widely different properties. See, for example, Owens (1995) *Physiol. Rev.* 75:487-517 (reference AQ on the Form 1449 submitted to the Patent and Trademark Office on July 20, 2004). This review teaches that mature VSMC proliferate at an extremely low rate and are almost completely geared for contraction, expressing a unique repertoire of contractile proteins, ion channels, and signaling molecules that clearly distinguish mature VSMC from any other cell type. In contrast, the principal function of VSMC during

vasculogenesis is proliferation and production of matrix components of the blood vessel wall. Thus, the Owens review teaches that proliferative and contractile VSMC are two very different cell types that express different groups of genes. The Grainger *et al.* patent discloses only that tamoxifen has an effect on proliferative VSMC. Since the Grainger *et al.* patent fails to provide support for the notion that tamoxifen would affect the contractile activity of mature VSMC, a person having ordinary skill in the art reading this reference would not have been motivated to use tamoxifen to normalize vasoconstriction of endothelially-compromised VMSC, because there would have been no reasonable expectation of success.

Further, Applicant's specification teaches that the effect of tamoxifen on VSM was not firmly established even after the Grainger *et al.* patent was filed. See, for example, the sections of Applicant's specification at page 2, lines 12-15 and extending from page 26, line 21 to page 27, line 11. These sections disclose that at the time the present application was filed, the inventor believed that norepinephrine-induced contraction of normal vasculature (i.e., vasculature having an intact endothelium) was not affected by tamoxifen treatment. These sections further disclose that due to the lack of effect on normal VSM, the inventor did not previously examine the effect of tamoxifen on endothelially-compromised VSM. In addition, these sections of the specification also disclose that Applicant's previous findings were published as Lamb and Barna (1998) *Am. J. Physiol.* 275:H151-H160, and Lamb and Barna (1998) *Am. J. Physiol.* 275:H161-H168 (both included on the Form 1449 mailed to the Patent and Trademark Office on June 18, 2001). Thus, as of 1998, the effect of tamoxifen on normal VSM was uncertain. Due to this uncertainty, a person of ordinary skill reading the Grainger *et al.* patent would not have had a reasonable expectation that tamoxifen would affect VSM associated with vasculature having a compromised endothelial layer.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 1, 6-11, and 23 under 35 U.S.C. § 103(a).

The Examiner rejected claim 25 under 35 U.S.C. § 103(a) as being unpatentable over the Grainger *et al.* patent as applied to claims 1, 6-11, and 23 above and further in view of U.S. Patent No. 5,470,883 (the Stromberg patent). The Examiner stated that the Grainger *et al.* patent does not teach that norepinephrine causes the contractile response of vasculature as set forth in

claim 25, but that the Stromberg patent teaches a method of inhibiting or reversing the peripheral vasoconstrictive effect of norepinephrine by oral administration of tamoxifen citrate. Thus, the Examiner concluded that it would have been obvious to one of ordinary skill in the art to employ tamoxifen to normalize the contractile response of vasculature comprising a vascular smooth muscle cell layer and a compromised endothelial cell layer caused by norepinephrine, because Stromberg teaches that tamoxifen is useful for reversing (normalizing) the vasoconstrictive effect of norepinephrine and because Grainger *et al.* teach that tamoxifen is useful for inappropriate or pathological activity of vascular smooth muscle cells and endothelial cells.

Applicant respectfully disagrees. Claim 25 recites a method to normalize the contractile response of vasculature in response to a vasoconstrictor agonist in a patient in need of such normalization. The cited patents fail to suggest such a method. As discussed above, "inhibiting" contraction is not the same as "normalization" of contraction. Neither the Grainger *et al.* patent nor the Stromberg patent suggests using tamoxifen to normalize the contractile response of vasculature in response to a vasoconstrictor agonist such as norepinephrine. In fact, the Office Action mailed on March 23, 2004, by which time both the Grainger *et al.* patent and the Stromberg patent were of record, included the following statement by the Examiner at pages 4 and 5:

> . . . there do not appear to be any examples or teachings in the prior art wherein a compound similar to the claimed compounds was administered to a subject to normalize the response to any vasoconstrictor (emphasis in original) . . . given the lack of . . . prior art regarding normalizing in response to a vasoconstrictor agonist (emphasis added) . . .

Given these statements, the Examiner appeared to believe, at least as of March 2004, that the prior art fails to teach or suggest using an agent such as tamoxifen to normalize contraction in response to a vasoconstrictor such as norepinephrine, as recited in claim 25. Since neither the Grainger *et al.* patent nor the Stromberg patent suggests using tamoxifen to normalize contraction, the combination of these references fails to render claim 25 obvious.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claim 25 under 35 U.S.C. § 103(a).

CONCLUSION

Applicant submits that claims 1, 6-11, 23, and 25 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Applicant believes that no fee is due. Please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

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